On the otherhand, US Patent No. 6,329,350 (van Borstel *et al.)* relates to the use of pyrimidine nucleotides precursors in the treatment of sepsis. The rationale for treatment being that pyrimidine nucleotides can protect the liver from endotoxin- related toxicity in sepsis. It is suggested that since severe infections like sepsis and hepatitis can lead to liver damage through depletion of nucleotides, supplementation with pyrimidine nucleotides can a have a beneficial effect.

Similarly US Patent No. 5,470,838 and US Patent No. 5,583,117 (van Borstel *et al.)* relate to the methods and use of delivering exogenous uridine and cytidine to assist the cellular repair or regeneration processes by providing the optimum nutritional and biochemical environment conducive to restoration of normal metabolic function. Since many important metabolic reactions can be functionally subsaturated and limited by availability of various substrates or co-factors, one could assist the normal repair process by providing an optimum supply of nutrients and co-factors see Borstel et al., '117, lines 30-45.

However, physiological effects attained by restoration of a normal nutritional status are vastly and totally different from pharmacological interventions based on an understanding of the etiology of acute and chronic inflammation. It is well know that depletion of essential nutrients or trace elements can have devastating effects on normal physiology and metabolism. E.g., it is well know that Retinol (Vitamin A alcohol or esters) is essential for growth, the development and maintainance of epithelial tissue and for vision. Vitamin A deficiency occurs when dietary intake is low and may result in xeropthalmia or dry eye. However, administration of Isotretinoin, the cis configuaration of tretinoin, which is the acid form of Vitamin A had unforeseen pharmacological effects when utilized in the treatment of acne and certain neoplastic disorders (Martindale, The extra pharmacopiea 30th edition). Restoration of a

temporary deficiency state can therefore result in certain foreseeable effects since many symptoms of a deficiency state are reversible. It is, however, erroneous to conclude that evidence of a beneficial effect of exogenous uridine and cytidine in assisting tissue repair functions automatically implies that the same substances would be therapeutically effective at acute and chronic inflammatiory conditions with completely diverse clinical picture and etiology.

Bacterial/Viral infections have not been reported to be involved in the etiology of a number of diseases covered by the present invention, including reperfusion injury, cancer, coronary heart disease, arteriosclerosis, restenosis after coronary angioplasty, asthma, rheumatoid arthritis and IBD including ulcerative colitis, Crohn's disease and psoriasis. Therefore, knowledge of a protective effect of uridine in bacterial sepsis cannot automatically lead to the deduction that this substance could be of benefit in diseases with vastly different etiology and clinical picture. Otherwise once could, in a similar vein, conclude that since uridine has already been used in the treatment of hereditary orotic aciduria, a condition leading to uridine deficiency, it would be obvious to anyone skilled in the art that uridine could be used for the treatment of other conditions when a similar depletion occurs (Girot R, Hamet M, Perignon JL, Guesnu, M, Fox RM, Cartier P, Durandy A, Griscelli C. Cellular immune deficiency in two siblings with hereditary orotic aciduria,. New. Eng. J. Med. 1983, 700-704. and Becroft DMO, Phillips LI, Simmonds A. Herditary orotic aciduria and megaloblastic anaemia: a second case, with response to uridine. Br. Med. J. 1965, 1: 547-52.).

The *systemic inflammatory response syndrome* (SIRS), as defined recently by critical-care specialists, may have an infectious or a noninfectious etiology. Systemic inflammatory response syndrome as defined by critical care specialists should fulfill at least 2 of the

following conditions: (1) oral temperature > 38°C or < 36°C; (2) respiratory rate of > 20 breaths /min; (3) heart rate of > 90 beats/min; (4) leukocyte count of >12 000 /ul or < 4000 /ul. If infection is suspected or proven, a patient with SIRS is said to have sepsis. Sepsis can be a response to any class of microorganism. The septic response is usually triggered when microorganisms spread from the gastrointestinal tract or skin into contiguous tissues. Localized tissue infection may then lead to bacteremia or fungemia. Alternatively, microorganisms may be introduced directly into the bloodstream (for example, via intravenous catheters). In a minority of cases, no primary site of infection is apparent. Although thrombocytopenia occurs in 10 to 30 percent of patients, the underlying mechanism(s) are not understood. Platelet counts are usually very low (Harrison's Principles of internal medicine, 14th edition, Vol.1, 776-780.).

Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of acute viral hepatitis are caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV). A sixth agent, hepatitis G virus (HGV), has been discovered, but its role in acute viral hepatitis remains to be established. All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma, common to the bloodborne types (HBV, HCV, and HDV), on the other (Harrison's Principles of internal medicine, 14th edition, Vol.2, 1677-1704.).

and the airway epithelium itself potentially are an additional source of mediators to enhance both the immediate and the cellular phase (Harrison's Principles of internal medicine, 14th edition, Vol.2, 1419-1426.).

Inflammatory bowel disease (IBD) is a general term for a group of chronic inflammatory disorders of unknown cause involving the gastrointestinal tract. Chronic IBD may be divided into two major groups, chronic nonspecific *ulcerative colitis* (UC) and *Crohn's disease* (CD). Clinically these disorders are characterized by recurrent inflammatory involvement of intestinal segments with diverse clinical manifestations, often resulting in a chronic, unpredictable course. The causes of UC and CD remain unknown. In UC, there is an inflammatory reaction primarily involving the colonic mucosa. Crohn's disease, in contrast to ulcerative colitis, is characterized by chronic inflammation extending through *all layers of the intestinal wall* and involving the mesentery as well as regional lymph nodes (Harrison's Principles of internal medicine, 14th edition, Vol.2, 1633-1645.).

Atherosclerosis refers to the thickening of the arterial intima (*sclerosis*, "hardening") and accumulation of lipid (*athere*, "gruel") that characterize the typical lesion. Although many generalized or systemic risk factors predispose to its development, this disease preferentially affects certain regions of the circulation. Atherosclerosis of the coronary arteries commonly causes angina pectoris and myocardial infarction. Atherosclerosis of the arteries supplying the central nervous system frequently provokes transient cerebral ischemia and stroke. In the peripheral circulation, atherosclerosis can cause intermittent claudication and gangrene and can jeopardize limb viability Involvement of the splanchnic circulation can cause mesenteric ischemia and bowel infarction. Taken together, experimental results in animals and studies of human atherosclerosis suggest that the "fatty streak" represents the initial lesion of

atherosclerosis. The formation of these early lesions probably results from focal accumulation of lipoproteins in regions of the intimal layer of the artery. Recruitment of leukocytes is the second step in formation of the fatty streak. A number of adhesion molecules or receptors for leukocytes expressed on the surface of arterial endothelial cells likely participate in the recruitment of leukocytes to the nascent fatty streak. Adhesion molecules of particular interest in this regard include vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) and P-selectin (Harrison's Principles of internal medicine, 14th edition, Vol.1, 1345-1380.).

Finally, Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. One view is that the inflammatory process in the tissue is driven by the CD4+ T cells infiltrating the synovium. Although there are a variety of systemic manifestations, the characteristic feature of RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of the synovial inflammation to cause cartilage destruction and bone erosions and subsequent changes in joint integrity is the hallmark of the disease. Despite its destructive potential, the course of RA can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, whereas others will have a relentless progressive polyarthritis with marked functional impairment. The cause of RA remains unknown. Microvascular injury and an increase in the number of synovial lining cells appear to be the earliest lesions in rheumatoid synovitis. The nature of the insult causing this response is not known. Rheumatoid synovial endothelial cells express increased amounts of various adhesion molecules involved in this process. Although this pathologic picture is typical of RA, it also can be seen in a variety of other chronic

inflammatory arthritides (Harrison's Principles of internal medicine, 14th edition, Vol.2, 1880-1888.).

The pathology of RA evolves over the duration of this chronic disease. The earliest event appears to be a nonspecific inflammatory response initiated by an unknown stimulus. The pathogenesis of rheumatoid and experimental arthritis involves migration of neutrophils from blood vessels into synovial tissues. Inflammatory mediators released by the neutrophils are partly responsible for the persistent inflammation, chronic recruitment of effector cells and erosion of articular cartilage associated with Rheumatoid arthritis (9). A recent report has demonstrated that P- and E-selectin act together with CD 18 and VLA-4 to mediate migration of neutrophils to sites of chronic inflammation (Birner, U., T.B. Issekutz, and A.C. Issekutz, The role of selectins in VLA-4 and CD18-independent neutrophil migration to joints of rats with adjuvant arthritis. Eur J Immunol, 1999. 29(4): p. 1094-100.).

The predominant infiltrating cell is the T lymphocyte. CD4+ T cells predominate over CD8+ T cells and are frequently found in close proximity to HLA-DR+ macrophages and dendritic cells. Subsequently, an initial, and perhaps specific, response of CD4+ T cells is induced that amplifies and perpetuates the inflammation. The presence of activated T cells can induce polyclonal B cell stimulation and the local production of rheumatoid factor. As tissue damage occurs, additional autoantigens are revealed and the nature of the T cell response broadens as additional clones of CD4+ T cells are recruited to the inflammatory site. Finally, as a result of persistent exposure to the inflammatory milieu, the function of synovial fibroblasts is altered and they may acquire destructive potential that no longer requires stimulation from T cells or macrophages (Harrison's Principles of internal medicine, 14th edition, Vol.2, 1880-1888.).

These findings have suggested that the propagation of RA is an immunologically mediated event, although the original initiating stimulus has not been characterized.

Uridine and hemostasis:

The normal hemostatic system limits blood loss by precisely regulated interactions between components of the vessel wall, circulating blood platelets, and plasma proteins. Effective primary hemostasis requires three critical events: platelet adhesion, granule release, and platelet aggregation. Most of the *inherited* plasma coagulation disorders are due to defects in single coagulation proteins, with the two X-linked disorders, factors VIII and IX deficiency, accounting for the majority of the congenital coagulation disorders. *Acquired* coagulation disorders are both more frequent and more complex, arising from deficiencies of multiple coagulation proteins and simultaneously affecting both primary and secondary hemostasis. The most common acquired hemorrhagic disorders are (1) disseminated intravascular coagulation (DIC), (2) the hemorrhagic diathesis of liver disease, and (3) vitamin K deficiency and complications of anticoagulant therapy. DIC can be either an explosive and life-threatening bleeding disorder or a relatively mild or subclinical disorder. Although there is a long list of diseases complicated by DIC, it is most frequently associated with obstetrical catastrophes, metastatic malignancy, massive trauma, and bacterial sepsis. In each case, a tentative triggering mechanism has been identified. For example, tumors and traumatized or necrotic tissue release tissue factor into the circulation, while endotoxin from gram-negative bacteria activates several steps in the coagulation cascade.

Although congenital and acquired bleeding disorders are relatively rare, venous and arterial thrombosis and embolism are common medical disorders that have been recognized for

thrombocytopenia occurs in 10 to 30 percent of septic patients, the underlying mechanism(s) are not understood. As the septic response becomes more severe, thrombocytopenia worsens, often with prolongation of the thrombin time, a decrease in fibrinogen, and the presence of D-dimers, suggesting DIC. However, US Patent No. 6329350 neither suggests nor provides evidence suggesting that pyrimidine nucleotides can inhibit platelet aggregation and thus provide a basis for prevention of thrombosis in patients with vascular disease and with a history of thromboembolism.

In conclusion, it would be obvious from a description of the etiology and pathogenesis of the above diseases that knowledge of a protective effect of uridine in sepsis would by no means lay the basis for an *a priori* conclusion that uridine should be beneficial in all other diseases with a component of acute or chronic inflammation.

4-thio-uridine (all claims)

Since initial binding of leukocytes to endothelium initiates the inflammatory process, an in vitro adhesion assay for random screening of substances that can block leukocyte adhesion to endothelial cells have been used. A variety of substances were tested as literature has shown that a number of, both, carbohydrate and non-carbohydrate structures can block interaction of selectins with cognate ligands. Screening of various chemical entities resulted in identification of three compounds, Isomalitol, Uridine and 4-Thiouridine, that could block adhesion of neutrophils. Although uridine and 4-thiouridine are related, the compounds have different chemical structures. Thus discovery was serendipitous in nature and not due to methodical structural manipulation using Uridine as a template. We do not agree with the statement that limited data from the use of uridine in bacterial sepsis can be extrapolated to any other related

cells present in BAL. Differential counts showed that there was a significant reduction in macrophages/monocytes, eosinophils and neutrophils in BAL of 4-thiouridine treated rats as compared to controls. Levels of TNF alpha, a major mediator of inflammation, in BAL were also reduced upon treatment with 4-thiouridine.

In view of the foregoing, it is believed that the amended independent claim and the claim dependent there from are in proper form. The Applicants respectfully contend that Von Borstel et al. U.S. 5,586,117 does not anticipate the claimed invention under the provisions of 35 U.S.C. § 103. Thus, claims 6 and 7 are considered to be patently distinguishable over the prior art of record.

The application is now considered to be in condition for allowance, and an early indication of same is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment and a clean copy of the specification page 7. The attached pages are captioned **"Marked-Up Copy of Amended Claims"** and **"Clean Copy of Specification page 7"**. Also attached hereto, please find the previously referenced Table 1 and Table 2.

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6. (Amended) A method for treatment of acute or chronic inflammations, and/or problems in hemostasis related to platelet function,

characterized in that a therapeutically effective amount of one or more the of compounds of the croup consisting of 4-thiouridine, isomaltitol, and uridine in the preparation of therapeutically effective compositions against acute or chronic inflammations with the exception of the use or uridine in the treatment of inflammatory conditions caused by a bacterial infection is administered to a subject in need of such treatment.

7. (Amended) The method according to claim 6, wherein the active compound is administered in such an amount that the serum concentration thereof is 0.1 to 100 mM.